Etravirine (ETR, Intelence, TMC 125)

For additional information see Drugs@FDA:
http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm

Formulations

Tablets: 100 mg and 200 mg

Dosing Recommendations

Neonate/infant dose:
ETR is not approved for use in neonates/infants.

Pediatric (6-11 years of age) dose:
ETR is not approved for use in children. Investigational dose currently in Phase II trial is 5.2 mg/kg (maximum 200 mg) twice daily in children ≥6 years of age.

Adolescent (12-17 years of age) dose:
ETR is not approved for this age group. Preliminary data from the Phase II trial (5.2 mg/kg, maximum 200 mg, twice daily–see Pediatric Use section) showed lower exposure than adults.

Adult dose (antiretroviral [ARV]-experienced patients):
200 mg twice daily following a meal.

Selected Adverse Events

- Nausea
- Rash including Stevens-Johnson syndrome
- Hypersensitivity reactions (HSRs) characterized by rash; constitutional findings; and sometimes organ dysfunction, including hepatic failure, have been reported.

Special Instructions

- Always administer ETR following a meal. Area under the curve (AUC) of ETR is decreased by about 50% when the drug is taken on an empty stomach.
- ETR tablets are sensitive to moisture; store at room temperature (59–86°F) in original container with desiccant.
- Patients unable to swallow ETR tablets may disperse the tablets in a small amount of water. Instruct patients to stir the dispersion well and consume it immediately. The glass should be rinsed with water several times, and each time the rinse water should be swallowed completely to ensure that the entire dose is consumed.
- **Dosing of ETR in patients with hepatic impairment:** No dosage adjustment is necessary for patients with mild-to-moderate hepatic insufficiency. No dosing information is available for patients with severe hepatic impairment.
- **Dosing of ETR in patients with renal impairment:** Dose adjustment is not required in patients with renal impairment.

Metabolism

- Metabolism by cytochrome P450: inducer of cytochrome P450 3A4 (CYP3A4) and inhibitor of CYP2C9 and CYP2C19. Substrate for CYP3A4, 2C9, and 2C19. Also inhibitor of p-glycoprotein (Pgp).
- Multiple drug interactions (see below).

Drug Interactions (See also the Guidelines for the Use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents.)***:***

- *Metabolism:* Etravirine is an inducer of CYP3A4; an inhibitor of CYP2C9 and CYP2C19; and a substrate for 3A4, 2C9, and 2C19. Etravirine is also an inhibitor of Pgp.
- Etravirine is associated with multiple drug interactions.
- Before etravirine is administered, the patient's medication profile should be carefully reviewed for potential drug interactions with etravirine.
- Etravirine should not be coadministered with the following ARVs: tipranavir/ritonavir, fosamprenavir/ritonavir, atazanavir/ritonavir, unboosted protease inhibitors (PIs), nevirapine, or efavirenz.

Major Toxicities:

- *More common:* Nausea, diarrhea, mild rash. Rash occurs most commonly in the first 6 weeks of therapy. Rash generally resolves after 1 to 2 weeks on continued therapy. A history of non-nucleoside reverse transcriptase inhibitor (NNRTI)-related rash does not appear to increase the risk of developing rash with etravirine. However, patients who have a history of severe rash with prior NNRTI use should not receive etravirine.
- *Less common:* Peripheral neuropathy, severe rash including Stevens-Johnson syndrome, HSRs (including constitutional findings and sometimes organ dysfunction including hepatic failure), and erythema multiforme have been reported. Discontinue etravirine immediately if signs or symptoms of severe skin reactions or HSRs (including severe rash or rash accompanied by fever, general malaise, fatigue, muscle or joint aches, blisters, oral lesions, conjunctivitis, facial edema, hepatitis, eosinophilia) develop. Clinical status including liver transaminases should be monitored and appropriate therapy initiated. Delay in stopping etravirine treatment after the onset of severe rash may result in a life-threatening reaction. It is recommended that patients who have a prior history of severe rash with nevirapine or efavirenz not receive etravirine.

Resistance: The International Antiviral Society-USA (IAS-USA) maintains a list of updated resistance mutations (see http://www.iasusa.org/resistance_mutations/index.html) and the Stanford University HIV Drug Resistance Database offers a discussion of each mutation (see http://hivdb.stanford.edu/pages/GRIP/ETR.html).

Pediatric Use: Etravirine is not Food and Drug Administration (FDA) approved for use in children and the pharmacokinetics (PKs), safety, and efficacy of etravirine in pediatric patients have not been established. Pediatric experience with etravirine is limited and pediatric trials are under way.

A Phase I dose-finding study involving 21 children, 6–17 years of age, with virologic suppression on a stable lopinavir/ritonavir-containing regimen compared doses of 4 mg/kg twice daily and 5.2 mg/kg twice daily using both an investigational 25-mg formulation and the available 100-mg formulation[1]. Etravirine therapy was added for 1 week and PK sampling and analysis were performed. Given the concern for underdosing in children and the lack of a safety signal in this study, the higher 5.2-mg/kg twice-daily dose is currently being studied in a Phase II trial[2] in pediatric patients.

The week 24 population PK data from this Phase II trial (101 treatment-experienced children 6-17 years of age) revealed lower etravirine exposures in adolescents (12-17 years of age) compared to 6-11 year old children and to adults (see table below).

	Median AUC_{12} (ng*h/mL)	Median C_{0h} (ng/mL)
Children 6-11 years of age (N=41)	5,289	342
Adolescents 12 to 17 years of age (N=60)	3,775	236
Adults (DUET study)	4,380	299

Of note, 93% of the adolescents were receiving the adult dose of etravirine (200 mg twice a day).

Despite insufficient data to recommend a pediatric dose, etravirine is being used in the salvage therapy setting in pediatrics. A report describing 12 heavily treatment-experienced, perinatally infected children who were monitored as part of the French Expanded Access Program (200 mg twice daily, range 2.8–5.3 mg/kg twice daily; median age 15 years, range 12–17 years) demonstrated good tolerability and virologic responses[3]. Similar results were seen in a study of 23 patients (median age 14.2 years) in Spain[4]. Median follow-up was 1 year in both studies.

An analysis of genotypic and phenotypic HIV resistance profiles in 35 children from a Ugandan clinic with clinical failure of a first-line regimen containing an NNRTI other than etravirine demonstrated reduced etravirine susceptibility (fold-change >2.9) in 35% of samples.

References

1. Konigs C, Feiterna-Sperling C, Exposito S, et al. Pharmacokinetics and dose selection of etravirine in HIV-infected children between 6 and 17 years, inclusive. Paper presented at: 16th Conference on Retroviruses and Opportunistic Infections (CROI); February 8-11, 2009; Montreal, Canada. Abstract S-167.
2. Kakuda TN, Green, B., Morrish, G., et al. . Population pharmacokinetics of etravirine in HIV-1-infected, treatment-experienced children and adolescents (6 to < 18 years). 3rd International Workshop on HIV Pediatrics, July 15-16, 2011. Abstract # PP_1.
3. Thuret I, Chaix ML, Tamalet C, et al. Raltegravir, etravirine and r-darunavir combination in adolescents with multidrug-resistant virus. *AIDS.* 2009;23(17):2364-2366.
4. Briz V, Palladino C, Navarro M, et al. Etravirine-based highly active antiretroviral therapy in HIV-1-infected paediatric patients. *HIV Med.* 2011.